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Review

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INNOVATIVE THERAPIES REDEFINE TREATMENT GOALS IN MULTIPLE SCLEROSIS

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SUMMARY – The treatment of multiple sclerosis (MS) is becoming more complex, especially with the expanding number of available therapies for relapsing forms of MS. Greater understanding of the degenerative aspects of MS pathogenesis is redefining treatment goals and creating new treatment strategies. The existing immunomodulation drugs (disease-modifying therapies, DMTs) used in MS treatment have shown only partial benefits in controlling disease progression, primarily by reducing the inflammation component. However, new therapies for MS have been shown to be effective in delaying disease progression by protecting against brain atrophy, which is considered the most important preindicator of future patient disability. The favorable effect on reducing brain atrophy suggests the potential neuroprotective or even neuroregenerative effects of new treatments, marking progress in the treatment of MS.

Key words: *Multiple sclerosis – therapy; Multiple sclerosis, relapsing-remitting – drug therapy; Immunosuppressive agents – therapeutic use; Treatment outcome*

The Risk of Multiple Sclerosis

If left untreated, multiple sclerosis (MS) is a devastating disease with multiple negative impacts on patient health. If we consider that quality of life is a multidimensional category comprised of functional, emotional, social and spiritual elements of health, it is evident that the negative impacts of MS are manifested in all aspects of the patient's quality of life (Fig. 1).

Some indicators of the negative impacts of MS on the quality of life pertain to increased unemployment, divorce and solitary life, and suicide. Life expectancy of an untreated MS patient is by about 8 years shorter than of persons without MS. The quality of life of those suffering from MS is inversely proportionate to the Expanded Disability Status Scale (EDSS) score. Approximately 50% of MS patients become unemployed when they reach an EDSS score of 3 and/or after 10 years of receiving the diagnosis[1,2].

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Multiple Sclerosis Pathogenesis: Is It an Inflammatory or Primarily Degenerative Disease?

Multiple sclerosis is considered an autoimmune, demyelination and neurodegenerative disease of the central nervous system with a biphasic course that causes a wide spectrum of neurological and psychological symptoms.

The paradigm of the MS pathogenesis is still a topic of discussion and debate among controversial positions. The currently established stance in which MS is an autoimmune process led by an inflammatory demyelination disease counters the theory that MS is actually a neurodegenerative disease, either primary or associated with age[4]. Research has shown that there is support for both scenarios and that the 'demyelination syndrome' implies various types of damage, which suggests a range of mechanisms involved in their de-

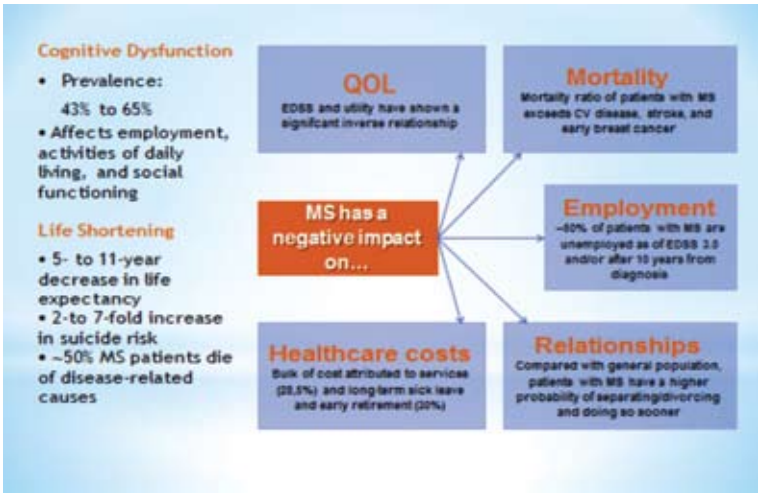

Fig. 1. Untreated multiple sclerosis is a devastating disease[3].

velopment. In addition to focal demyelination, MS is characteristic due to the diffuse appearance of damage to normal-appearing white matter (NAWM), axonal damage that can be of varying intensity, and brain atrophy[5,6]. The acute phase of the disease is marked by focal demyelination with post-contrast imbibitions, while the progressive phase of the disease is dominated by atrophy of the brain and loss of axons, which is correlated with the degree of neurological disability.

The relapsing-remitting form of MS (RRMS) is classically considered a biphasic disease with relapses of a potentially reversible phase of the disease, correlated with inflammatory demyelination and a secondary potentially irreversible phase of the disease that is marked by critical axon loss. Inflammatory changes are less pronounced in the later phases, although the disease shows increasing progression. This dissociation between the intensity of inflammation and the progressive development of neurological disability represents the inflammatory-neurodegenerative paradox that is characteristic of MS, and which marks transition to the irreversible phase of the disease. Numerous clinical, neuropathological and neuroimaging studies have aimed to define mutual associations of the inflammatory and progressive phases of MS. It has long been known that early relapse impacts the long term disability in MS[7], although there are still uncertainties and ambiguities as to the trigger that switches RRMS to the secondary progressive form. Some epidemiological studies of the natural course of MS have shown certain limitations regarding the effects of the inflammatory phase of the disease on the progression of disability, giving a conclusion that the relapsing and neurodegenerative phases of MS are mutually independent. In such a case, not only the number of relapses can have predictive value in the development of disability; age, sex, residual deficit after first relapse, time to second relapse, total number of relapses in the first two years and duration of the inter-relapse interval can also be valuable indicators[8-11]. Although the position on the influence of relapses on the progression of the disease is controversial, it is unquestionable that MS ultimately results in an unsustainable progressive phase with permanent disability of the patient[12]. The dual concept of the pathogenesis of MS significantly determines the start of treatment.

When discussing the treatment of MS, it is important to always emphasize the importance of taking an individual approach, for many reasons, i.e. the complexity of MS pathogenesis implies a high inter-individual variability of the course of the disease; immunomodulation drugs have varying mechanisms of activity with high variability of therapeutic response; and there is a multitude of treatment algorithms, and selecting the right one should be adapted to the needs of each individual patient.

No Evidence of Disease Activity (NEDA) – A New Goal of Multiple Sclerosis Treatment

Until recently, it was considered that MS was regulated to a satisfactory level with the achievement of reduction in the number of relapses, a reduced number of new lesions visible on magnetic resonance imaging

(MRI), and slowing progression of patient disability. Today, the bar for treatment goals has been raised substantially higher, and new treatments are expected to completely halt the activity of the disease and prevent the emergence of patient disability, as only such a treatment outcome will result in complete wellbeing of the patient.

The course of MS has changed since the advent of disease-modifying agents. These new drugs provide many benefits for patients, including fewer and less severe relapses, better recovery after relapses, prevented or postponed progression of disability, reduced accumulation of disease burden or decreased brain lesion activity, and improved quality of life, cognitive functioning or less fatigue. This has led to evolving treatment goals, with wellbeing of the patient being now an important consideration in the therapeutic contract (Fig. 2).

No evidence of disease activity (NEDA) was first reported as a concept in 2009[13]. This new treatment goal implies a state of complete absence of disease activity, and represents a new concept in the treatment of MS, in which the imperative becomes 'zero tolerance' of its activity. NEDA has been defined as a composite consisting of:

- absence of relapses
- no sustained EDSS score progression
- no new or enlarging T2 or T1 gadolinium--enhancing (GAD) lesions on annual MRI

No evidence of disease activity may become a key outcome measure of disease-modifying therapy (DMT) for MS patients, as well as a potential treat-to-target goal, according to a new study. Up to 40% of patients achieve NEDA in 2 years with currently available drugs, but disability progression may be confounded by previous injury (Fig. 3)[14].

Fig. 2. Treatment goals are evolving in multiple sclerosis.

Treating to target requires individualized planning of treatments and assessment in each patient, taking into account severity, recovery from relapses and lesion characteristics. Unresolved issues in individualizing treatment include optimal definition of NEDA and breakthrough disease, incomplete assessment, and integration of NEDA with treatment risks.

Research has shown that the share of NEDA patients in placebo controlled studies is consistently higher in patients receiving therapy than those on placebo after two years of monitoring. The exception was the CARE MS II study, in which alemtuzumab showed to be superior in relation to interferon beta 1a s.c. (Rebif) as the active comparator[13] (Fig. 3).

Predictivity of Treatment Response

One of the greatest challenges in the treatment of patients with MS is the ability to predict treatment outcome. Response to treatment is highly heterogeneous among MS patients and therefore predictors of response to treatment are needed to optimize patient management.

Which patients will be responders, and which will be non-responders? The assumption is that 20% of 100 treated patients will have an optimal treatment response (as responders), 40% will have a suboptimal treatment response (partial responders), and 40% will have an unsatisfactory treatment response (non-responders) (Fig. 4).

Can we identify subgroups of patients who show different treatment effects? Clinical, MRI and biological parameters can all define the predictivity of response to treatment. A later age at onset, lower disability and lower number of GAD lesions at baseline MRI were predictors of treatment efficacy.

Early detection of nonresponders, i.e. patients without a satisfactory treatment response to the administered treatment, in which the disease shows an increased level of activity, is very important in order to begin another type of treatment for those patients that will prove more effective (Fig. 5).

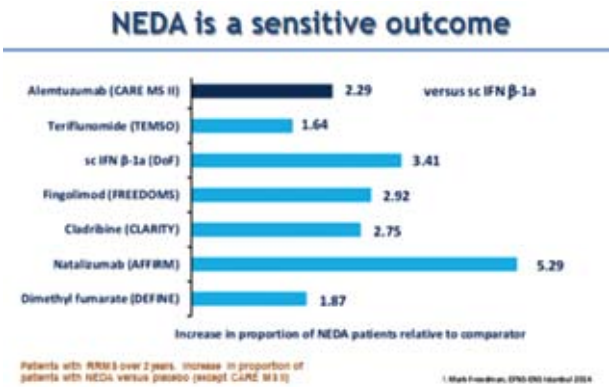

Fig. 3. No evidence of disease activity (NEDA) status in patients with relapsing-remitting multiple sclerosis (RRMS) over two years.

A later age at onset, lower disability and lower number of GAD lesions at baseline MRI were predictors of treatment efficacy[15]. However, it is not clear whether these parameters are really predictors of treatment response or prognostic factors. The risk of disability is greater in patients with increased MRI activity[16,17]. Brain atrophy measurement is not always a reliable measure, due to technical difficulties and bias during the acquisition and data analysis phases[18]. Clinical evaluation and MRI studies together could be more useful in defining the prognosis (Fig. 6).

Brain Atrophy in Multiple Sclerosis – The Iceberg Analogy

Multiple sclerosis is usually referred to as an 'iceberg disease'. There are research notes looking at the difference between clinical and subclinical MS relapses that refer to them as MS icebergs. Visible damage, such as relapse and clinical progression, is just the tip of the iceberg, while the 'invisible' damage, such as brain atrophy, is much more dangerous, as it can sneak up and cause patient disability.

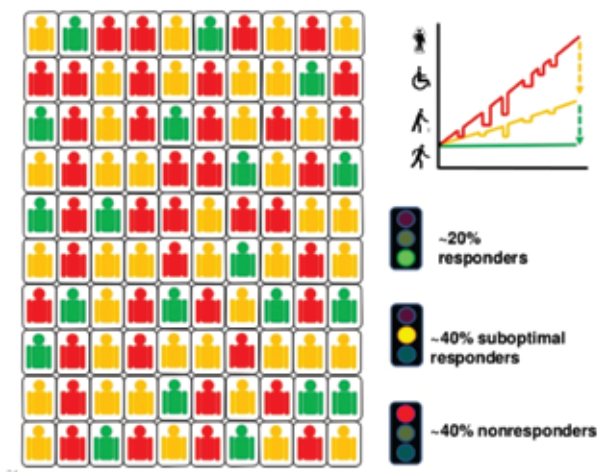

Fig. 4. Out of 100 multiple sclerosis patients: who are responders?

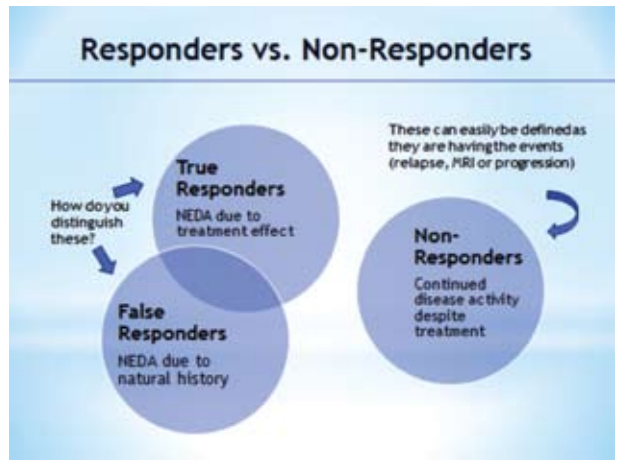

Fig. 5. Responders versus non-responders.

Brain atrophy is a relevant surrogate marker of disease progression in MS because it represents the net effect of various pathological processes leading to brain tissue loss. It has been shown to correlate with cognitive impairment, EDSS and quality of life[20-22]. Brain atrophy seems to be a widespread process that is present in all stages of MS, even it can be seen as early as a clinically isolated syndrome[23,24]. Several studies have demonstrated that, on average, brain volume decreases by 0.7%-1% yearly in patients with MS[25], which is approximately three-fold the rate in normal controls. Although both gray matter and white matter undergo atrophy, it has been suggested that loss of gray matter is a more sensitive marker of the neurodegenerative process in MS than whole brain atrophy[26]. Furthermore, some *in vivo* data have suggested that the rate of gray matter volume loss accelerates as the disease progresses[27]. Gray matter volume appears to be a very clinically meaningful MRI metric; a recent multicenter study in 977 patients at all stages of MS found gray matter volume to be a better predictor of disability and cognitive impairment, as measured by the EDSS and paced auditory serial addition test, respectively, than white matter volume or white matter lesions[28]. Similarly, gray matter volume correlated

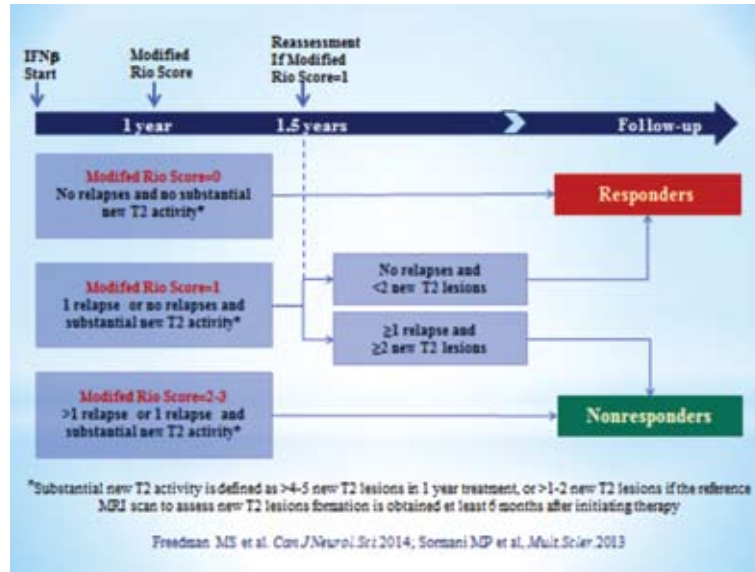

Fig. 6. Monitoring algorithm for assessment of clinical response[19].

better with quality-of-life measures than white matter or whole brain volume[21].

The ideal method for measuring brain volume loss in MS has not been determined. Segmentation-based methods include the commonly used brain parenchymal fraction (BPF) and its variants, index of brain atrophy and whole brain ratio. BPF is defined as the brain parenchymal volume divided by the volume within the surface of the brain. The BPF uses an algorithm to detect the outer surface of the brain and the amount of brain tissue within that outer surface, essentially subtracting out (segmenting out) the ventricular cerebrospinal fluid volumes. BPF has been shown to correlate moderately well with disability[29].

Therapies that in clinical trials have shown a positive effect on reducing the rate of brain volume loss are natalizumab, fingolimod and alemtuzumab.

Natalizumab (NTZ) treatment significantly decreases cortical lesion accumulation and cortical atrophy progression in severe RRMS[30]. Investigation of atrophy data from a pivotal natalizumab trial has demonstrated an increased rate of volume loss compared to placebo after the first year of therapy. It was considered to probably be due to a pseudoatrophy effect. Early brain volume loss during natalizumab therapy is mainly due to white matter fraction (WMF) volume loss and it is related to the inflammatory activity present at therapy initiation. The pseudoatrophy effect is mostly due to white matter volume changes[31] and it has been held responsible for the lack of net impact of natalizumab on brain volume outcomes in 2-year trials, but no data are available beyond 24 months[32].

Fingolimod (FGL) is the only oral therapy with a consistent, early and held on reducing the loss of brain volume (brain volume loss, BVL). Consistent effect of fingolimod to reduce BVL was demonstrated in three controlled phase 3 clinical trials[33-36]. Improvements in outcomes related to cognition and BVL occurred within 6 months of fingolimod treatment initiation[37,38].

Alemtuzumab (AZB) is the first and currently only MS therapy to demonstrate sustained improvement in preexisting disability *versus* an active comparator (interferon beta 1a s.c.)[13].

Treatment Strategy

The selection of an optimal treatment for MS is becoming an even greater challenge considering the growing number of new treatments available (Fig. 7).

The existing immunomodulation drugs (DMTs) have been proven to have only partial benefits in controlling the progression of the disease, primarily by reducing the inflammation component. However, new treatments are offering to provide protection against BVL, which is of critical importance, as brain atrophy is today considered one of the most significant

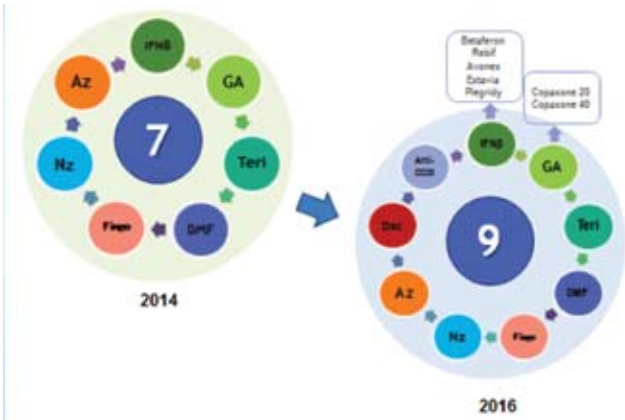

Fig. 7. Treatment complexity.

preindicators of future patient disability.

In line with the phrase 'time is brain', the treatment of MS should begin early and it should be effective, as it is only possible to prevent conversion to the secondary progressive form of the disease that is marked by permanent disability through an early start to treatment.

Early treatment can delay relapses, disability, and BVL at long term. The case for early treatment is based on the 'window of opportunity' to prevent irreversible axonal damage. Early treatment will prevent the irreversible damage to the nervous system, which occurs very early and is (at least partially) related to inflammation in MS. It is also well known that the early course of the disease influences long term outcomes. Immunomodulatory treatments can reduce the inflammation that predominates in the early phases of the disease, and patients with greater clinical activity during their first year of treatment were at an increased risk of continuing with relapse and/or sustained disability in the next two years[39]. Data from several clinical trials show that treatments for MS are more effective in the relapsing remitting phase than in the progressive phase of the disease[40].

The traditional approach to treating MS implies commencing with a treatment of moderate efficacy, and in the case of unsatisfactory treatment response and persistence of active disease, a shift is made to the high and very high efficacy treatments.

However, it is important to stress that the high and very high efficacy treatments can also be the first choice treatment for patients with very active or rapidly progressing forms of the disease (Figs. 8 and 9).

Escalation treatment and induction treatment are two different algorithms in the treatment of MS. In escalation treatment, the safety profile of the treatment is the top priority, whereas in induction treatment the priority is efficacy and prompt halting of disease progression, even with increased treatment risk. Therefore, induction treatment is primarily intended for patients with very active and particularly rapidly progressing forms of the disease, who are threatened with rapid development of disability.

The choice of initial agent is influenced by factors relating to the agents themselves, the severity of the onset of the patient's disease, and patient-specific factors such as medical comorbidities, reproductive status, and tolerance for risk. The decision must be based on careful consideration by the physician and discussion with the patient, taking many potential issues into account and realizing in some cases there is no clear 'best' choice[42]. MS patients are now active players in the decision-making process; patients are having ever greater input into the decision making process surrounding their disease management. Their perception of the disease and the treatment response is a key component of MS management.

Timing of therapy for all currently available MS DMTs relates to the prevention of acute inflammation and relapse, including prevention of development of new lesions on MRI. Ultimately, the true goal is to prevent the development of disability, including long term disability related to progressive disease, as described above. Starting DMT early in the MS disease course has been shown to have a beneficial effect on relapse prevention, and appears to curtail the atrophy

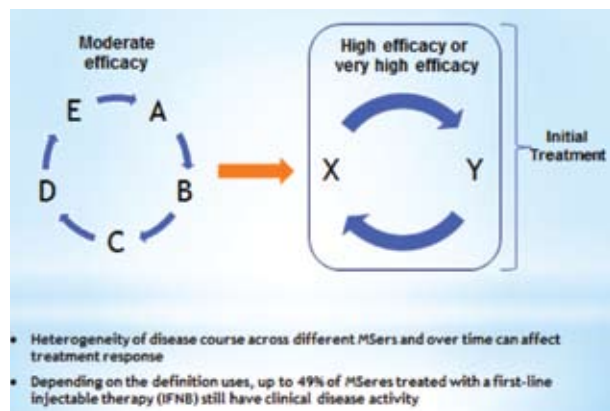

Fig. 8. Traditional approach to multiple sclerosis treatment[41].

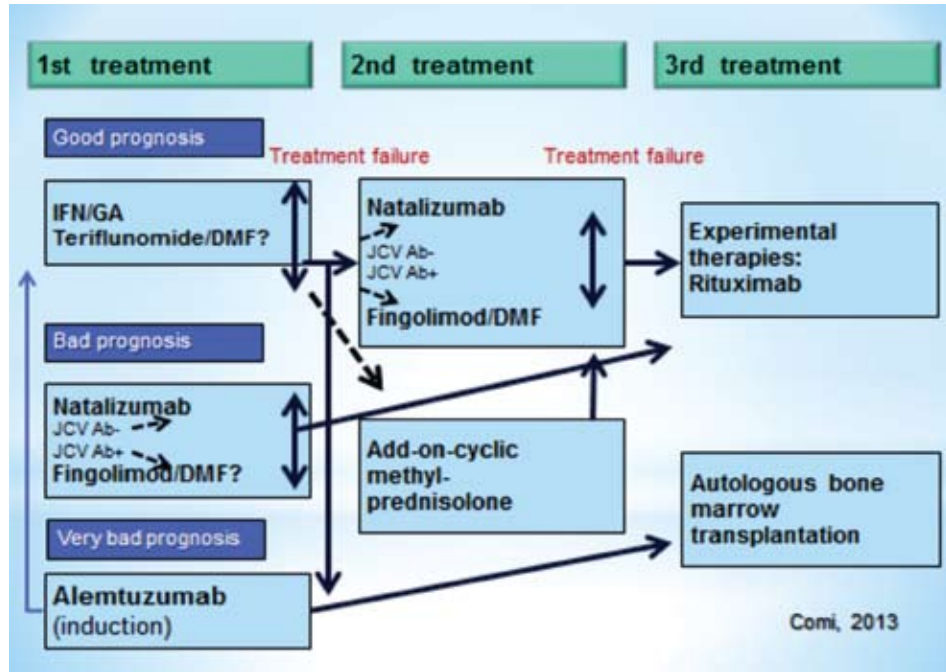

Fig. 9. Algorithm for treatment of relapsing multiple sclerosis.

and neurodegenerative changes that are now known to begin at disease onset[42].

New treatments are more innovative and likely one step closer to an ideal treatment that implies not only absence of any disease activity, but also maximum safety, excellent tolerance, maintenance of work capabilities and quality of life for the patient. Once this level of treatment excellence has been achieved, we may be able to speak of having a possible cure for MS (Fig. 10).

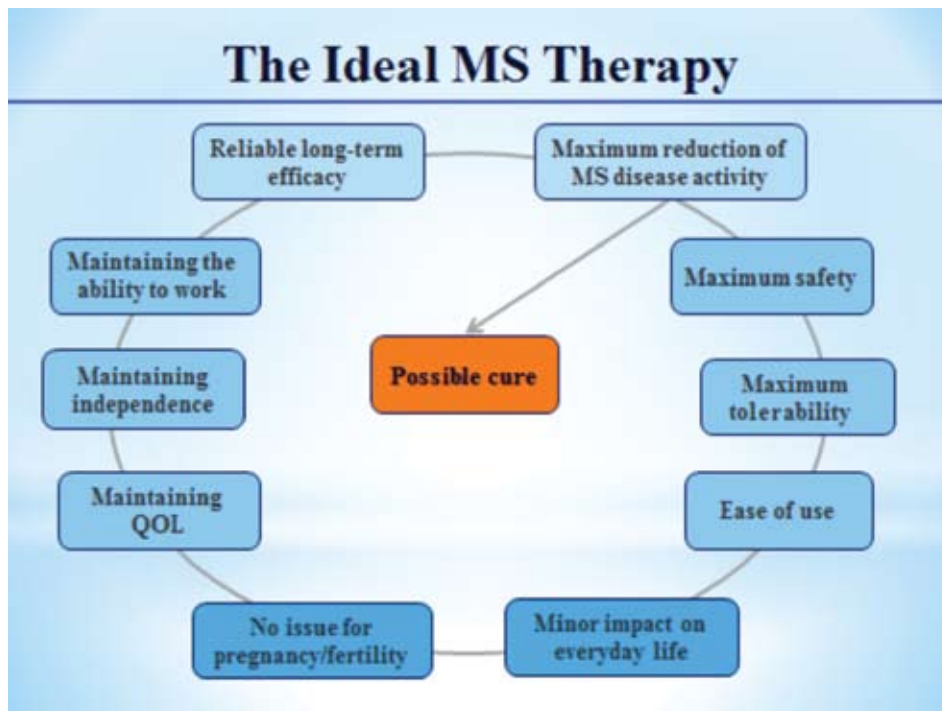

Fig. 10. The ideal multiple sclerosis therapy

Fig. 10. The ideal multiple sclerosis therapy.

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Sažetak

INOVATIVNE TERAPIJE REDEFINIRAJU TERAPIJSKE CILJEVE U MULTIPLOJ SKLEROZI

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Liječenje multiple skleroze (MS) postaje sve složenije, naročito zbog rastućeg broja dostupnih terapija za relapsni oblik MS. Sve bolje razumijevanje degenerativnog aspekta patogeneze MS redefinira terapijske ciljeve i stvara nove terapijske strategije. Dosadašnji imunomodulacijski lijekovi (*disease-modifying therapies,* DMTs) u terapiji MS pokazuju samo djelomičnu korist u kontroli progresije bolesti, prvenstveno smanjujući upalnu komponentu. Međutim, nove terapije u MS pokazuju djelotvoran učinak na odgađanje progresije bolesti štiteći od atrofije mozga koja se smatra najvažnijim predskazateljem budućeg invaliditeta bolesnika. Pozitivan utjecaj na smanjenje atrofije mozga ukazuje na potencijalno neuroprotektivno ili čak neuroregenerativno djelovanje novih terapija, što predstavlja korak naprijed u liječenju MS.

Ključne riječi: *Multipla skleroza – terapija; Multipla skleroza, recidivirajuće-remitentna – farmakoterapija; Imunosupresivna sredstva – terapijska primjena; Ishod liječenja*